We are studying how membrane trafficking pathways are regulated in interphase and mitotic cells. In particular, we are focusing on two major aspects of Golgi-mediated transport events: (I) the interface between lipid homeostasis and Golgi secretory function, and (II) the mechanism by which membrane trafficking events to, through, and from the Golgi apparatus are regulated in mitotic cells.

**Lipid homeostasis and membrane trafficking**

A major challenge in current cell biology research is to understand the mechanisms that maintain the lipid distribution among and across cellular membranes. The unique lipid composition of the Golgi complex is critical for maintaining its structural and functional identity (Lev, 2006). Yet, the underlying mechanisms that maintain critical levels of certain lipids in the Golgi membranes remain poorly understood. Currently, we found a novel mechanism for maintaining a critical level of diacylglycerol (DAG) in the Golgi apparatus and demonstrated its essential role for Golgi secretory function in human cells (Litvak et al., 2005). We showed that depletion of the phosphatidylinositol (PI)/phosphatidycholine (PC)-transfer protein, Nir2, leads to substantial inhibition of protein transport from the Golgi apparatus to the plasma membrane due to impaired fission of transport carriers at the Golgi membranes (Fig. 1). We also found that knockdown of Nir2 reduces the level of DAG in the Golgi complex by facilitating its conversion into PC. These results show for the first time that a PI/PC-transfer protein regulates the level of a key lipid in the Golgi apparatus in mammalian cells, and demonstrate the interface between lipid homeostasis and Golgi secretory function.

More recently, we found that several lipid-transfer proteins (LTPs), including Nir2, are shuttled between the Golgi apparatus and the endoplasmic reticulum (ER), and are probably involved in the regulation of lipid homeostasis in these organelles. Interestingly, all these LTPs contain a similar ER-targeting determinant that mediates their interaction with the same integral ER-membrane protein (Amarilio et al., 2005). We believe that these LTPs function interdependently to locally control the level of certain lipids in the ER and/or the Golgi complex, thereby regulating membrane trafficking events through these organelles. We are currently investigating this hypothesis.

**Membrane trafficking during cell division**

In addition, we are studying how membrane trafficking events are regulated in dividing cells. The process of cell division ensures the segregation of chromosomes and cellular organelles into daughter cells. The Golgi apparatus is extensively fragmented...
into thousands of vesicles and tubules early in mitosis. These morphological changes coincide with the blockage of membrane transport to and through the Golgi complex. Late in mitosis, however, the Golgi reassembles and membrane trafficking events are concomitantly restored (Lev, 2005) (Fig. 2A). Although these morphological changes have been well characterized, the underlying molecular mechanism of mitotic Golgi fragmentation remains largely unknown. The involvement of key mitotic kinases, such as Cdk1 (Cyclin dependent kinase) and Plk1 (Polo like kinase 1) in mitotic Golgi disassembly was demonstrated in different experimental settings, and several mitotic Golgi phosphoproteins have already been found. Indeed, we found that the peripheral Golgi protein Nir2 is phosphorylated by Cdk1 during mitosis, dissociates from the Golgi complex and translocates to the cleavage furrow (Fig. 2b), where it interacts with Plk1 in a Cdk1-phosphorylation dependent manner. We further showed that this interaction is required for cleavage furrow ingression and cytokinesis completion (Litvak et al., 2002 & 2004). Our results support the new concept that mitotic Golgi disassembly is required for the dissociation of peripheral Golgi proteins, and that this dissociation is critical for coordinating the behavior of Golgi membranes, chromosomes and the cytoskeleton during mitosis. Inhibition of mitotic Golgi disassembly and/or reassembly blocks normal mitosis progression, which is crucial for maintaining genomic integrity, and avoiding cellular transformation, neoplasia, or cell death.

Our current challenge is to understand the mechanisms that regulate the Golgi structure and secretory function in mitotic cells, and to experimentally examine the concept that the partitioning of cellular organelles is coordinated with chromosome segregation to ensure the production of daughter cells following mitosis. To this end we apply multidisciplinary experimental approaches including, a proteomic approach aimed at identification of mitotic Golgi phosphoproteins, live-cell imaging, in vitro Golgi disassembly/reassembly assays and a variety of advanced molecular and cell biology studies.

Fig. 2 A. Mitotic fragmentation of the Golgi complex in mammalian cells is attributed to blockage (blocked arrows) of membrane trafficking events to and from the Golgi apparatus. Nevertheless, budding of secretory vesicles from the Golgi complex is continued. B. The distribution of Nir2 (red) and the medial Golgi protein NAGT-I (green) in interphase, late anaphase and late telophase. The localization of Nir2 in the cleavage furrow and midbody during cytokinesis is marked by an arrow. Bar, 10 μm.

Selected publications

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